MATERIALS AND METHODS FOR DIAGNOSIS, PREVENTION AND/OR TREATMENT OF STRESS DISORDERS AND CONDITIONS ASSOCIATED WITH ABETA PEPTIDE AGGREGATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application Ser. No. 61/194,064, filed Sep. 24, 2008, and U.S. Provisional Application Ser. No. 61/099,746, filed Sep. 24, 2008, each of which is hereby incorporated by reference herein in its entirety, including any figures, tables, nucleic acid sequences, amino acid sequences, and drawings.

BACKGROUND OF THE INVENTION

[0002] Post-traumatic stress disorder (PTSD) is a type of anxiety disorder that manifests after exposure to a life-threatening traumatic event (Kessler (2000); Kessler et al. (1995)). PTSD affects approximately 6.8% of the American population and is caused by rape, assault, accidents or combat (Kessler et al. (2005)). In 2004, a US army study of more than 3600 veterans returning from Afghanistan and Iraq found that the percentage of veterans suffering from PTSD and related disorders, was 9.3% for those who served in Afghanistan and 17.1% for those who were stationed in Iraq (Hoge et al. (2004)). Compared with normal individuals, PTSD patients have a reported higher utilization of medical services (Calhoun et al. (2002); Solomon and Davidson (1997)), and are at increased risk for developing cardiovascular disease and cancer (Boscarino (2006); Schnurr and Jankowski (1999)).

[0003] Tobacco consumption is directly associated with PTSD. Numerous reports dealing with smoking among individuals with PTSD, mostly as a result of combat related trauma, showed that smoking prevalence is higher than in the normal population with rates ranging from 34% to 86%.

[0004] Alzheimer's disease (AD) is the main cause of dementia in the elderly and a progressive degenerative disease of the brain associated with advanced age. AD is characterized by the presence of extracellular amyloid senile plaques in the brain mainly consisting of amyloid-beta (Abeta or Aβ) peptide (that is generated by proteolytic processing of the trans-membrane protein amyloid precursor protein (APP)) and neurofibrillary tangles composed of aggregated tau protein (a microtubule associated protein). AD pathology is characterized at the neuronal level, by synaptic loss and cell death of selected neuronal populations (Echeverria and Cuello (2002)). There are approximately 17 million people affected by the disease world wide, and it is estimated that by 2050 there will be approximately 25 million affected in the United States. There are no effective therapeutic agents for this disease, new drugs and potential cures are being intensely investigated. According to many studies the aggregated form of Aβ and not the monomeric form of the peptide is toxic. One of the strategies being investigated as a potential cure for AD is the search for molecules that are able to stop Aβ aggregation. Thus, it is important to be able to detect Aβ peptide in animal tissue.

[0005] Currently, a diagnosis of Alzheimer's disease is generally made using a psychiatric evaluation in conjunction with magnetic resonance imaging of central nervous system (CNS) for changes in morphology. Definitive diagnosis of Alzheimer's disease can only be made by post-mortem neuropathological examination of a patient's brain. Thus, it would be beneficial to have a means for diagnosing and monitoring Alzheimer's disease in a patient in vivo.

[0006] Down's syndrome (DS), also named as chromosome 21 trisomy, is a genetic disorder caused by the presence of an extra 21st chromosome. DS is characterized by impairment of cognitive abilities and physical changes and other health problems such as a higher risk for congenital heart defects, recurrent ear infections, obstructive sleep apnea, and thyroid dysfunctions. The incidence of DS is estimated at 1 per 800 to 1,000 births. The adult patients with DS have much higher incidence of Alzheimer's disease than non affected individuals. It has reported that 25% of persons with DS develop the disease by age 40, and the rate increases dramatically to 65% after age 60. Post-Mortem, nearly all adults that suffered from DS showed Alzheimer's disease pathology.

[0007] Tobacco smoke is composed of thousands of compounds, most of which have deleterious actions on cell homeostasis resulting in toxic effects over the cardiovascular, pulmonary and brain systems (Gallinat et al. (2006); Yolton et al. (2005)). Despite all of these negative actions, several studies suggest that smoking is protective against AD (Court et al. (2005); Merchant et al. (1999); Birtwistle and Hall (1996)) and Parkinson's disease (Hong et al. (2009)). The benefits of tobacco have been attributed to nicotine, an alkaloid and a potent cholinergic agonist present in tobacco (Doolittle et al. (1995); Levin (2002)). Nicotine has anti-apoptotic actions by a mechanism dependent on nicotinic acetylcholine receptors (nAChRs), and has neuroprotective activity against Aβ toxicity in vitro (Gahring et al. (2003)). Using the transgenic mouse model of AD, Tg2576 (APPswe) (Hsiao et al. (1996)), it has been shown that nicotine reduces the levels of Aβ in the brain and improves memory abilities in these mice (Nordberg et al. (2002); Unger et al. (2005); Hellstrom-Lindahl et al. (2004)). However, the short half-life, toxicity and potential negative effects in promoting tau pathology of nicotine discouraged its use in therapeutics (Oddo et al. (2005)).

[0008] Nicotine is metabolized to cotinine in the liver (Hammond et al. (1991)), which has a longer half-life than nicotine (10-24 h vs. 2-3 h, respectively) and similar cytoprotective activity (Terry et al. (2005)). The molecular mechanisms underlying the protective actions of cotinine are not well understood. Cotinine is a weak agonist at the nicotinic and muscarinic ACh receptors (mAChR), and it does not have significant cholinergic effects in the brain (Terry et al. (2005); Buccafusco et al. (2007); Briggs et al. (1995)).

[0009] In search of a mechanism of tobacco protection against AD, the effect of nicotine and cotinine on the aggregation of amyloidogenic fragments of Aβ peptides has been explored in previous studies (Salomon et al. (1996); Szymanska et al. (2007); Kirschner et al. (2008)). The first study reported by Salomon et al. (1996) showed by using circular dichroism (CD) and ultraviolet spectroscopic techniques that nicotine and also but at a less extent cotinine inhibited amyloid formation by $A\beta_{1-42}$ peptide. Also by using nuclear magnetic resonance (NMR) analysis of the Aβ-nicotine complex, they suggested that the biologically active optical enantiomer of nicotine (L-(−)-nicotine, S form) inhibited the conversion of the $A\beta_{1-42}$ peptide from its soluble form into insoluble β-sheet oligomers. The effect was attributed to the interaction of the $A\beta_{1-42}$ residues His6, His13 and His14 via aromatic π-π and/or electrostatic interactions with the pyrrolidine moieties of nicotine (Salomon et al. (1996)).